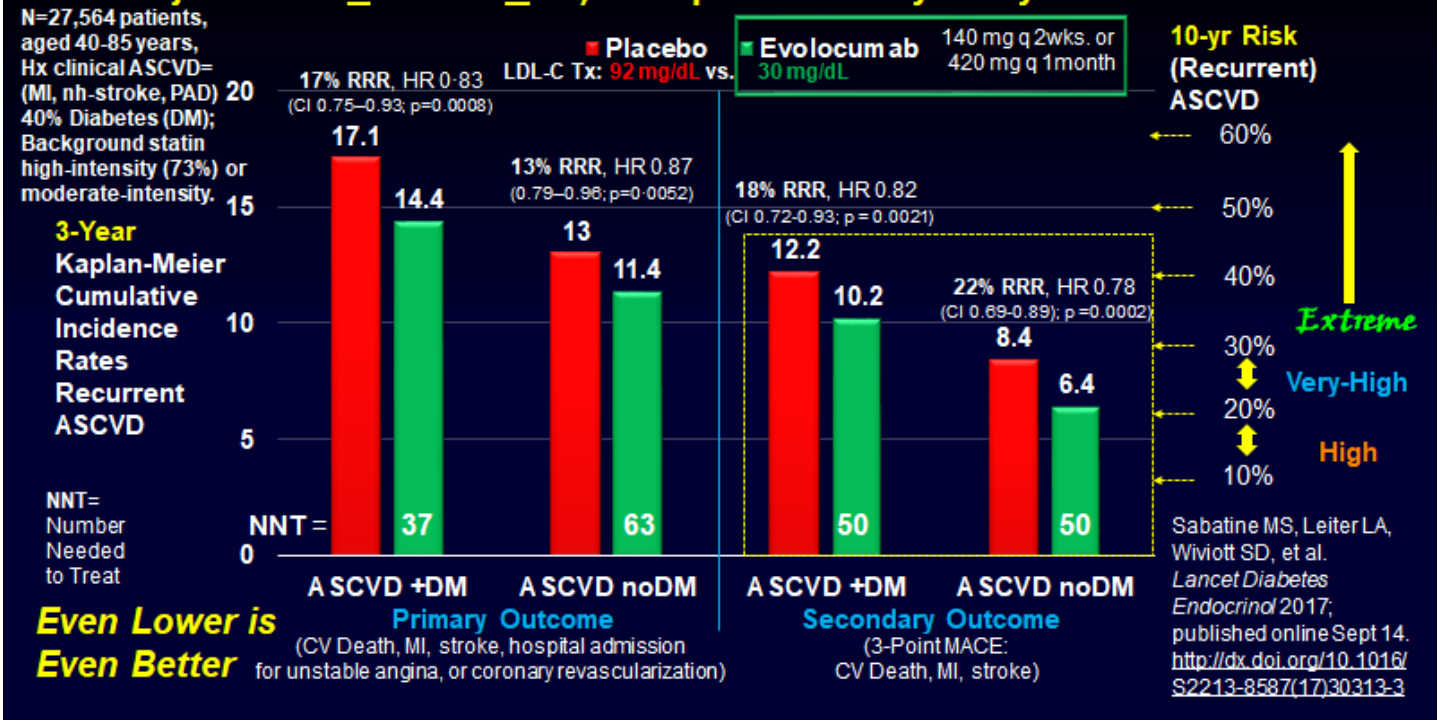
From the evidence-based-medicine (EBM) or strict-trialist point-of-view-approach **IMPROVE-IT (as an entire cohort)** suggests **ACS** is a setting in which when **targeting LDL-C, the goal should be <55 mg/dL**. EBM does not look at the subgroups. In the 2017 AACE Dyslipidemia Guideline, EBM was not strictly abided, as 'ACS' patients, were placed in the 'very high' risk category (10-year risk >20%), and the targeted LDL-C goal was <70 mg/dL; the not so lower goal presumably, because IMPROVE-IT suggested benefit exclusive to the 'Diabetes subgroup'. But the setting of 'ACS' is a most 'Extreme Risk' category with 10-year risk > 30% [see ACS trials: MIRACL, PROVE-IT, IMPROVE-IT].

Moving forward and keeping up with discovery (**FOURIER**), as usual, both groups achieve similar relative risk reduction, but because the absolute risk is higher among those with diabetes, the residual risk remains higher (that's why diabetes needs more 'extreme' risk reduction), relative to those without diabetes. However, in FOURIER, both 'multimorbidity' ("progressive") 'stable' ASCVD and 'morbidity' ('stable' ASCVD in single vessel/ arterial bed), with or without Diabetes, achieved benefit from lower LDL-C. Also, in FOURIER, the closer a trial participant was to ACS (i.e. less stable) the higher the event rate and the greater the risk reduction benefit (slide 26 Repatha speaker slide deck).

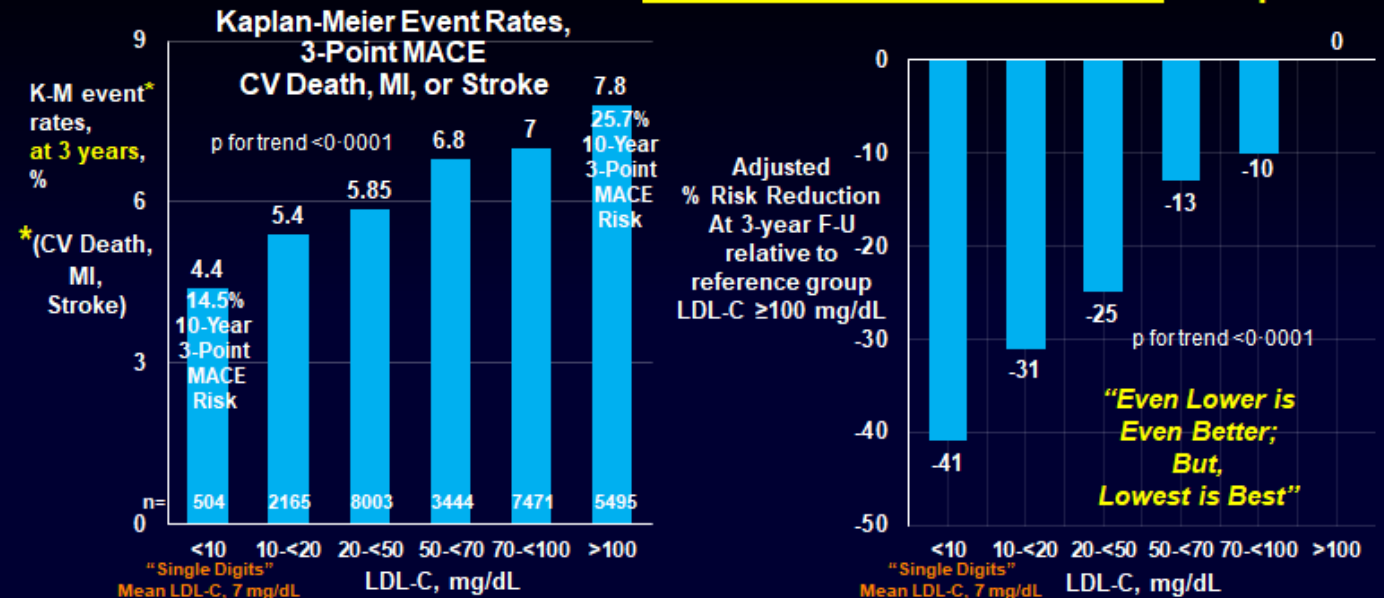
In those settings, FOURIER, supports a guideline that when **targeting LDL-C**, the **goal is <30 mg/dL (the EBM-entire Cohort), with no lower LDL-C limit (the subgroup analyses) [emphasis added]. These 2 statements counter the 2013 ACC/AHA notion that one backs off when an LDL-C <40 mg/dL is reached.** Does **AACE** need to wait until a 2019 guideline or algorithm publication or the ODYSSEY (alirocumab) outcome trial results, to make this **interim change** in **a position or statement/guideline, that could benefit patients now, i.e. sooner than 2019?** It would be great, but not necessary, to make this statement along with updated goals when targeting non-HDL-C (~60 mg/dL calc'd/estimated) and the atherogenic particle number as apo B (not available yet in any published FOURIER papers; only known info Apo B reduced 46% and between-group difference was 49%) and, since many physicians have this test performed, LDL particle number as LDL-P (a value that could possibly be extrapolated from looking at multiple studies). AACE can still make the 'targeted LDL-C goal statement' and just acknowledge that the adjusted FOURIER targeted Non-HDL-C, apo B, and LDL-P goals, at this point, are not known.

FOURIER (Further Cardiovascular OUtcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk): Prespecified Analysis by Diabetes Status



Sabatine MS, Leiter LA, Wiviott SD, et al. *Lancet Diabetes Endocrinol* 2017; published online Sept 14. http://dx.doi.org/10.1016/S2213-8587(17)30313-3

FOURIER: Prespecified Analysis of the Relationship between the achieved LDL-C Level at 4 weeks and the Risk of the Secondary Efficacy Composite* Endpoints



Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, Toth K, Gouni-Berthold I, Lopez-Miranda J, Schiele F, Mach F, Ott BR, Kanevsky E, Pineda AL, Somaratne R, Wasserman SM, Keech AC, Sever PS, Sabatine MS; for the FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet. 2017 Aug 25. pii: S0140-6736(17)32290-0. doi: 10.1016/S0140-6736(17)32290-0. & AHA 2017